THE THRESHOLD OF SKIN FLARE IN PERSONS WITH AND WITHOUT MALIGNANT NEOPLASTIC DISEASE*†

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INTRODUCTION

The threshold of pain is identified as the lowest intensity at which a noxious excitant when applied for an arbitrary time, such as one second, will produce a painful or a pricking sensation. *The threshold of the skin flare reaction* is identified as the lowest intensity at which a noxious excitant when applied for an arbitrary time, such as one minute, will cause a flare reaction or "blush" about the point of application of the excitant.

Since it is important to use an excitant which can be controlled and measured accurately, heat was used in this study. We have arbitrarily required the reddened area to measure at least 15 mm. in its largest diameter, when the area of contact of the excitant is not greater than 3 mm. in diameter. This requirement is established to avoid the possibility of confusing the local "red spot" or "red reaction," which occurs at the point of application of the noxious excitant, with the flare reaction. The flare reaction is a larger, more diffuse reddening and is due to a local nervous axon reflex resulting in a dilation of the blood vessels of the skin.

Considerable evidence indicates that the flare reaction is due to the release of histamine or a histamine-like substance (H-substance) at the point of contact of the noxious excitant (1). The H-substance presumably stimulates the sensory branch of an axon reflex which results in the vasodilation for one or more centimeters about the point of contact.

As a result of our general interest in the physiology of pain (2, 3, 4), we became interested in ascertaining whether a ratio exists between the threshold of pain and the threshold of flare. During the course of this study, it was found that patients with malignant neoplastic disease had an abnormally high threshold of flare as compared to clinically normal persons and to patients with arthritis who, like some cancer patients, suffered from rather severe pain. Our study on skin flare was then extended to determine to what extent a high threshold of skin flare is specific to malignant neoplastic disease.

METHODS

Apparatus No. I: The initial apparatus used for applying a graduated amount of heat to the skin was quite simple (Figure 1). The *applicator* was made of 26 gauge insulated nichrome wire. A single strand 4′6″ long was folded on itself to form a cord 27 inches long. The insulation was removed from the point of bending and this point of the wire was flattened to make an applicator tip with a "U" shaped contact with the skin of approximately 1:1:1

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millimeter. The two-ends of the applicator were connected in series with a 1.5 volt dry cell, a rheostat, and a milliammeter*.

Method of Performing the Test: To determine the threshold of pain, the current was turned on at a milliammeter reading of 400. The tip was allowed to heat in the air (room temperature) for 30 seconds, then brought into contact with the skin of the inner upper aspect of the forearm for 1 second (count 1001) and removed. This was repeated 5 times. The threshold of pain was taken as that milliammeter reading at which the subject reported a pricking pain on at least 2 out of 5 contacts. The reading usually ranged from 425 to 800 ma. in different subjects.

To determine the threshold of flare, the milliammeter reading was set at 600, and the tip of the applicator was allowed to heat in the air (room temperature) for 30 seconds. The tip was then placed into contact with the skin using only the pressure of its own weight, for one minute. If a flare did not occur at 600 ma., the current was increased to 625 ma., and then in increments of 25 ma. until a flare reaction was obtained. A new area of skin 2 or 3 cm. distant was used for each trial.

The threshold of flare was taken as that milliammeter reading at which a flare appeared about the contact of the tip. The flare must, and can easily be differentiated from the local "red spot" which occurs directly under the tip and is due to direct tissue injury.

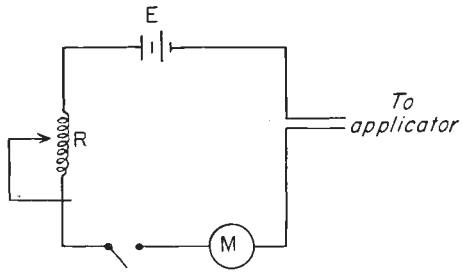


FIG. 1. Wiring diagram of Apparatus 1

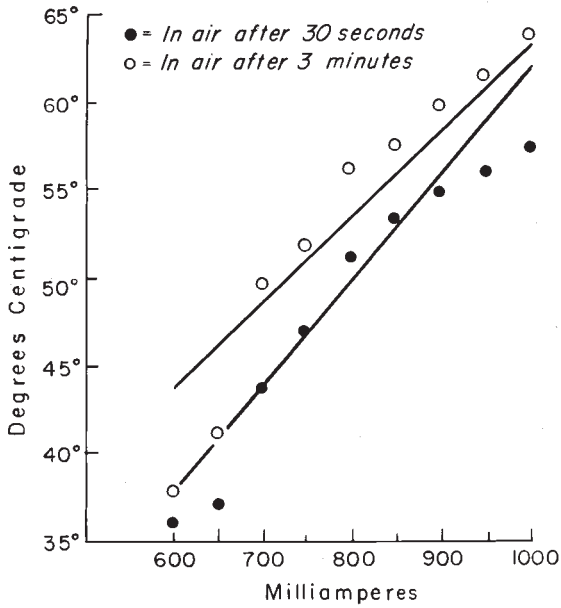
The skin of the inner upper aspect of the forearm and the skin of the back was used because it is known to be influenced relatively slightly by variations in blood flow and vasomotor nerve impulses (5). It is desirable to use the skin of the back as well as that of the forearm in patients with arteriosclerosis or other types of peripheral vascular disease. (In normal persons, the threshold of flare on the back is slightly lower than on the forearm.)

The milliammeter readings refer only to the particular apparatus we used. They would be applicable to another apparatus only if its electrical resistance or temperature of the applicator tip and its area of contact was the same. The approximate temperature of the tip of the applicator when set at 850 ma. is shown in Figure 4. The temperature of the applicator tip at various current intensities and under different uses is shown in Figure 2 A and B.

Apparatus No. II: The initial apparatus, though quite simple, did not permit a control of the various physical factors involved in producing the flare. For example, we did not know the temperature of the tip of the applicator before or after it made contact with the skin; we could not maintain a constant temperature of the heater; we did not know if the rate and amount of dissipation of heat might be more critical than the temperature at which flare occurred. Though the initial apparatus was adequate to show a difference in the threshold of flare between patients with and without cancer, it was inadequate for investigating the underlying physiological mechanisms.

Two instruments, Model A and Model B, were then made by Dr. Victor Guillemin of the Aeromedical and Physical Environment Laboratory of the University of Illinois. They were essentially the same, except that one was operated with a dry cell battery and the other with

* This apparatus was designed by Dr. Carl C. Pfeiffer, Department of Pharmacology, University of Illinois, for the study of the effect of drugs on pain threshold.



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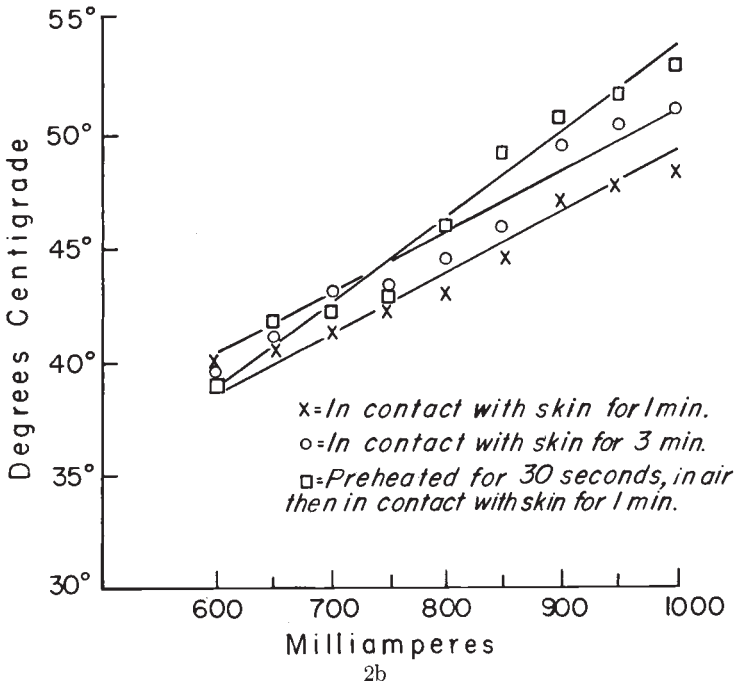

2b

FIGS. 2a and b. Temperature of the applicator tip of Apparatus 1 at various current intensities and under the conditions of different uses.

alternating current. The instruments were unique in that the applicator (Figure 3) to be applied to the skin contained an electrical heater and thermometer. If the temperature of the heater was maintained at a fixed level, the heat dissipation could be measured. If the

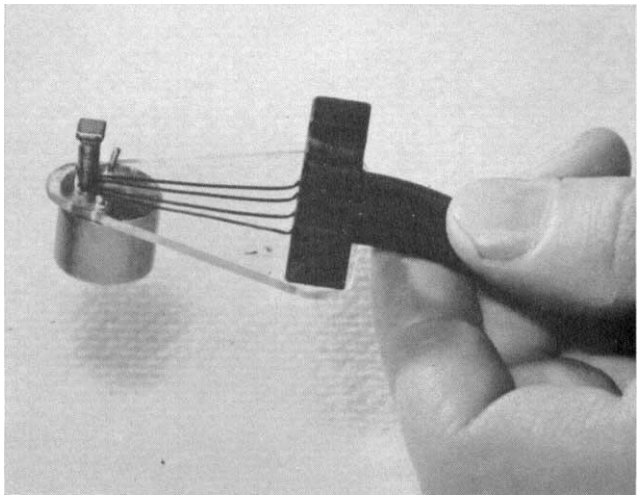

FIG. 3. Photograph of skin applicator

TABLE 1

Summary of tests on skin flare thresholds with apparatus no. 1

CONDITION	NO. OF CASES NORMAL TEST LESS THAN 850 ma.	NO. OF CASES ABNORMAL TEST 850 ma. OR MORE
Cases in which the interpretation of the results is certain		
1. Normal cases	77	0
2. Benign tumors	32	0
3. Non-tumor disease	340	0
Total	449	0
4. Proven malignant tumors	4	335
5. Superficial ca. of the skin	4	0
6. Secondary infection of a ca.	6	0
Total	14	335
7. Hodgkins disease	6	14
8. Brain tumors	5	8
9. Diagnosis of a possible, but not proven malignancy	0	9
10. Diagnosis of a non-malignant disease	0	8
11. Cancer diagnosis	5	0

A. Total cases = 853.
B. Cases proven to have or not to have a malignancy, items 1, 2, 3, 4, 5 and 6 = 798.
C. Total proven cases of ca. or non-ca. = 788.
D. Omitting cases under 5 and 6 = 798.
E. Including cases of Hodgkins with #1, 2, 3, 4, 5, 6 = 818.

heat energy was fixed, the thermometer gave the temperature of the heater at any given instant.

This apparatus has been described elsewhere (6) and will not be described here. The results are the same regardless of the heater used, but the readings in milliamperes differ

as these machines were handmade and no standardized equipment was used. This must be borne in mind in reading the data in the tables.

OBSERVATIONS MADE WITH APPARATUS NO. 1

The flare threshold of 913 subjects was determined, the test being repeated several times in most patients under approximately the same environmental

TABLE 2

Summary of the conditions in which the Skin Flare Threshold Test has been used, the initial apparatus no. 1 being employed, showing the difference of reaction of malignant and non-malignant disease

NON-MALIGNANT CONDITIONS	NO. OF CASES	THRESHOLD OF FLARE MILLI-AMPERES MEAN
1. Normals	77	747
2. Benign tumors	32	771
3. Non-malignant disease	340	769
Total non-malignant	449	761
MALIGNANT CONDITIONS		
4. Proven malignant diseases	339	902
5. Secondary infections of ca	6	775
6. Superficial skin cancer	4	781
Total	349	
7. Hodgkins disease	20	850
8. Brain tumors	13	844
Total	33	
Total malignant conditions	382	
9. Positive test with diagnosis of possible but not proven malignancy	9	
10. Positive test some some non-malignant disease	8	
11. Negative tests with a clinical diagnosis of cancer	5	
Total	12	
12. Patients with proven cancer but which are under active treatment	60	
Grand Total	913	

conditions (Table 1). Among the 913 subjects, 449 were known with considerable certainty not to have malignant disease, and 349 were known to have a histologically proven malignant tumor and were not under active x-ray or steroid therapy at the time of testing. Twenty patients with the proven diagnosis of Hodgkin's disease are considered separately. In 35 of the 913 patients (Table 2, items 8, 9, 10, 11) there was a question whether the tumor was malignant or whether the diagnosis of the non-malignant disease was correct. In the remaining 60 patients some type of active therapy was in progress.

It was observed that, if the threshold of flare was less than 850 ma. (the current required in Apparatus No. 1 to bring the applicator to the threshold temperature for flare), the patient very likely did not have a proven cancer. Using

TABLE 3

Showing types and numbers of patients with non-malignant disease who gave a threshold of flare in the non-malignant range with apparatus no. 1

	NUMBER	AVERAGE
Peptic ulcers	35	668.5
Diabetes mellitus	21	782.1
Endocrine	24	730.2
Liver diseases	18	766.6
Lung diseases	18	765.6
Heart diseases	21	765.5
Kidney diseases	6	779.2
Gastrointestinal disturbances	13	765.4
Hernia	11	747.7
Hemorrhoids	6	783.3
Skin diseases	9	729.0
Neurology	16	767.1
Tuberculosis (active)*	13	765.3
Arthritis	14	773.2
Allergy	10	765.0
Post-operative	10	747.5
Pregnancy	10	752.5
Arteriosclerosis	13	796.1
Pernicious anemia	14	783.9
Secondary anemia	8	787.5
Obesity	5	780.0
Blood discrasia	5	765.0
Brain injuries	8	775.0
Paraplegia	6	758.0
Inflammatory conditions	7	785.7
Peripheral vascular	9	750.0
Boek's sarcoid	2	800.0
Paget's disease	1	775.0
Cachexia	1	750.0
ACTH (arthritis & L.E.)	5	735.0
Total	340	

* Early cases.

this criterion, Table 2 was compiled to bring out this difference of reactivity between malignant and non-malignant disease.

In Table 2 it will be noted that a threshold indicating the absence of a malignancy was observed in 4 cases of superficial carcinoma of the skin and in 6 cases of pyogenic infection of a carcinoma. The low flare threshold in the patients with a brain tumor may have been due to the possibility that the brain tumors tend to be pathologically benign. The low value in Hodgkin's disease may have been

TABLE 4

Showing types and location of the cancer according to the organ

	NUMBER	AVERAGE
Stomach	35	926.4
Lungs	37	892.5
General carcinomatosis	12	923.3
Lower gastrointestinal tract	47	907.9
Internal organs	21	900.0
Uterus	15	896.6
Mouth	36	893.0
Lymphosarcoma Lympho-blastoma	15	878.3
Leukemia	18	925.0
Skin	27	887.0
Thyroid	11	866.8
Esophagus	10	883.0
Larynx, pharynx	10	893.0
Neuro-reticule sa.	6	896.0
Weing's sarcoma	2	900
Breast	21	902.3
Prostate	10	930
Others	2	925
Total	335	

TABLE 5

Showing the type of patient which gave doubtful or erroneous results

	NUMBER	RANGE
A. Positives without proven malignancy		
Patients without proven diagnosis	9	850+
Arteriosclerosis	2	850–1000
Pernicious anemia with icterus	1	1000
Hypertension	1	850
Foreign body in brain	1	850
Brain hemorrhage	1	850
Tabes dorsalis	1	950
Obesity	1	850
B. Negatives with apparent malignancy		
Patients without proven diagnosis of ca.	5	750–825
Cancer of the parotid gland*	1	725
Lymphosarcoma*	1	825
Cancer of the stomach, hermaphrodite*	1	800
Cancer of the naso-pharynx*	1	750

* These are unequivocal errors and are shown in Table 6, Item 4.

due to the known fluctuation of disease activity. Further study would be required to answer the questions raised by these discrepancies.

Table 3 shows the type of non-malignant diseases the "control patients" had, and Table 4 the location or type of malignancy which the "cancer patients" had. Table 5 shows the type of patients in which the flare threshold failed to indicate the absence or presence of a malignancy.

The results of the effect of treatment of the malignant disease on the flare threshold is shown in Table 6. It is to be noted that the administration of steroid hormones was quite consistently associated with a flare threshold characteristic of a non-malignant condition.

TABLE 6

Effect of treatment on the Skin Flare Test for malignant tumor disease using the initial apparatus (# 1)

TREATMENT	NO. OF CASES	THRESHOLD MILLIAMPERE		REMARKS
		Average	Range	
Ca. of breast receiving steroids	22	775	650–850	1 patient gave a positive test
Ca. of prostate receiving steroids	7	798	700–875	1 patient gave a positive test
1 to 4 hours after x-ray treatment of a cancer*	25	828	750–1000	
Surgically "cured" 1 to 5 years	16	797	725–850	1 not cured as per flare test
Total	70			
Minus 10 patients included in Table 2†	10			
Corrected Total	60			

* The x-ray treatment caused the test to be negative in 16 of the 25 patients. In some of the 16 patients this was of the nature of an immediate effect and in others of an accumulative effect indicating a destruction of the cancer.

† The 10 cases are subtracted because they were tested before x-ray treatment was started, and hence were included in the 339 cases in Table 2, Item 4.

The influence of age, sex, skin color, arteriosclerosis, hemoglobin concentration on the flare threshold

It was thought that age might influence the results because of changes in the blood vessels. In order to determine whether this supposition might be true the results on the non-cancer patients and cancer patients in Table 1 were distributed by decade. The results, shown in Table 7, indicate that age does not *significantly* affect the distribution. However, age *tends* to increase the threshold. The patients tested were taken as we saw them and without any attempt to have the same number in each group.

The results in Table 8 show clearly that sex has no marked effect on the skin flare reaction.

In patients with advanced *arteriosclerosis* the reading is more difficult to make. Therefore, more "false positives" occurred in patients with arteriosclerosis or

peripheral vascular disease than with any other disease (Tables 3 and 5). The reading becomes less difficult after one has performed over 100 tests and becomes experienced in reading the presence or absence of flare.

The reading was made with difficulty in *Negroes* because of the very dark skin. Therefore, we did not include many Negroes in this series of cases.

TABLE 7

Showing that the skin flare in cancer and non-cancer patients is not influenced by age to a significant extent

DECADE	NO. OF PATIENTS WITHOUT CANCER	MEAN THRESHOLD	NO. OF PATIENTS WITH CANCER	MEAN THRESHOLD
0–9	1	650	0	
10–19	21	713	0	
20–29	72	743	19	887
30–39	76	756	40	881
40–49	81	773	58	885
50–59	82	776	92	918
60–69	70	781	124	924
70–79	37	788	68	922
80–89	14	782	26	934

TABLE 8

The effect of sex on the skin flare reaction in patients with and without cancer

	TOTAL NO.	MALES		FEMALES	
		No.	Threshold	No.	Threshold
Normals	77	52	749	25	743
Benign tumors	32	29	770	3	775
Non-malignant disease	340	253	771	87	768
Total	449	334	759	115	762
Cancer	335	214	923	121	897
Hodgkin's disease	20	18	850	2	825
Brain tumors	13	13	844		
Secondary infection of cancer	6	6	775		
Skin cancer	4	3	775	1	825
Total	378	254	902	124	889
Grand total	827	588	822	239	821

Hemoglobin concentration of the blood did not render the reading difficult or inaccurate until the concentration was quite low, 3.5 grams per 100 cc. of blood or less.

OBSERVATIONS MADE WITH APPARATUS NO. 2

The Apparatus No. 2 is calibrated so that 0.01 ma. is equivalent to 0.2° C.

On the Use of Appratus No. 2: There are several methods by which the appa-

ratus No. 2 might be used. (I) The temperature of the applicator tip might be fixed in air, and the tip then applied to the skin and its temperature maintained regardless of the energy required to hold the applicator at a fixed temperature when in contact with the skin, or regardless of the rate of dissipation of heat chiefly by the skin temperature and blood flow. (II) The energy input might be fixed and maintained after applying the applicator to the skin without regard to the temperature of the tip. (III) The temperature of the applicator after applying it to the skin might be raised to a desirable level within a certain period of time at which level it is maintained. Since so little is known regarding the several factors that may be concerned in producing a flare with heat and their relative importance, all three possible methods had to be tried, and the best one selected on the basis of actual experimental results.

Method I. (a) The temperature of the applicator-tip is prepared at room temperature (ordinary room temperature in winter and summer is adequate, vide infra) during a period of 30 seconds by adjusting the heater current (meter C) until the desired temperature is obtained, which in Figure 2 was 44.5°C. (b) The applicator tip is then applied to the skin of the inner, upper aspect of the forearm for one minute during which time the temperature of the tip is maintained. Then, the tip is removed from contact with the skin. (c) If no flare or one measuring less than 15 mm. in its maximum diameter is obtained after waiting for 1 to 3 minutes, the procedure under "a" and "b" is repeated after increasing the heater current (meter C) so that the temperature of the tip is increased 0.4°C. or 0.02 ma. (meter B) at each subsequent trial, until no flare is observed. The first reading where flare (measuring at least 15 mm. in diameter) occurs is taken as the threshold.

Method II. (a) The applicator tip *without preheating* is applied to the skin and the heater current (meter C) is immediately set at 24 ma. This amount of current was selected because it heats the applicator tip while on the skin so that the temperature of the tip toward the end of the one minute period of application ranges between 43.4° and 49.4°F. (Figure 4, III) according to the individual subject. (b) After one minute the applicator tip is removed from contact with the skin. (c) If no flare is observed after waiting for 2 or 3 minutes, the heater current is increased at each subsequent trial by 1 ma. on the heater dial, or meter C. (d) If a flare is obtained and if its maximum diameter is more than 14 ma., the heater current is decreased at each subsequent trial by 1 ma. until the threshold is ascertained.

Method III. The applicator tip without preheating is applied to the skin and the heater current (meter C) is regulated so that after 15 seconds the temperature meter, or meter B, shows a reading of 0.52 ma., which is equivalent to a temperature of 45.8°C. (b) The temperature is then kept at this level for one minute, and then the applicator tip is removed from contact with the skin. (c) If no flare is observed after waiting for 2 or 3 minutes, the heater current (meter C) is increased so that the reading of the temperature meter (meter B) is increased 0.02 ma., or 0.4°C. at each subsequent trial until a flare of threshold size is obtained (15 mm.). (d) If a flare is obtained and if its diameter is more than 14 mm., the heater current is decreased so that the reading of the temperature meter is decreased 0.02 ma., or 0.4°C. at each subsequent trial until no flare of a threshold size (15 mm. or more) is obtained.

RESULTS OBTAINED FROM THE COMPARISON OF THE THREE METHODS

The results are summarized in Table 9. The data show that Method III is superior to the other methods. The accuracy of Method III approaches the accuracy of the initial method and apparatus.

Reference to Figure 4 shows how the method with Apparatus No. 1 and the three methods with the new Apparatus No. 2 vary as regards the mean temperature applied to the skin through the applicator tip and the energy input.

TABLE 9

Comparison of the 3 different methods of flare production with model B of apparatus no. 2

	CANCERS		CONTROLS		TOTAL		% ERRORS
	Right	Wrong	Right	Wrong	Cases	Errors	
1st method	82	10	89	16	171	26	15.2
2nd method	51	7	58	6	109	13	11.9
3rd method	160	2	87	4	247	6	2.4
Total	293	19	234	26	527	45	8.5

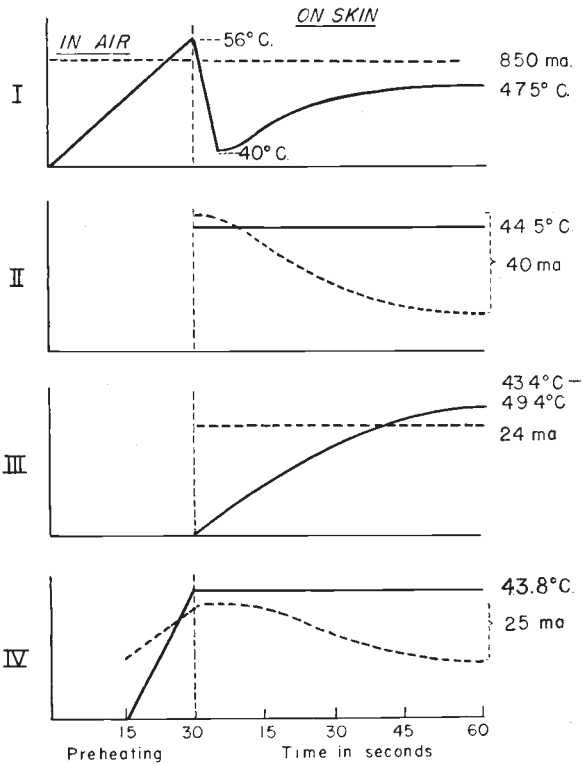

FIG. 4. Schematic comparison of the heat and energy factors of the different methods of application. In all figures the dotted lines represent energy and the solid lines heat.

No. I shows the old method. The temperature varies biphasically during the minute of application and the energy input is constant.

No. II shows the method I of application with the new apparatus. The temperature remains constant during the minute of application and the energy input is variable.

No. III. In method II of the new apparatus the temperature varies monophasically during the minute of application and the energy input is constant.

No. IV. In method III there is a 15 second preheating period on the skin. After that during the minute of actual stimulation the temperature remains constant and the energy varies monophasically over a comparatively small range.

A study of the diagrams in Figure 4 and the data in Table 2 and Table 9 in relation to the predictive value of the initial method and the three new methods

suggests that a relatively low mean temperature of around 44.0° C., applied for a minute, is critical in differentiating the flare threshold of patients with and without malignant neoplastic disease. The following procedure was followed when using Apparatus No. 2 for obtaining the data summarized under the "3rd method" in Table 9 and in making the observations in the remainder of this report.

SPECIFIC LIST OF INSTRUCTIONS FOR THE FLARE TEST

1. Turn on main switch M and adjust meter A with Knob 1 and 2 to 40 ma. This balances the instrument and should be checked occasionally between measurements.
2. Turn off switch M.
3. Place heating element on skin, holding it so that the pressure is purely that of its own weight.
4. Turn on main switch M and with the help of Knob 3 and 4 increase the energy input such that after 15 seconds meter B is on 0.52 ma. (45.8°C).
5. By control of energy with Knob 3 and 4 this level of 0.52 on meter B is maintained for one minute.
6. Turn off main switch M.
7. Read and measure with skin flare.
8. If no flare is present, repeat steps 3 to 7, while increasing the heat on meter B by steps of 0.02 ma., until a definite flare is observed.

If there is a definite flare repeat steps 3 to 7, while decreasing the heat on meter B in steps of 0.02 ma., until a threshold is established. (A flare with a maximum diameter of 15 mm. or definitely larger than the "red spot" under the applicator is required.)

THE VARIATION IN THE THRESHOLD OF FLARE IN THE SAME SUBJECT

Patients with and without malignant disease were systematically studied with Apparatus No. 2A.

The results in Table 10 show that no significant variation was found during the day. For example the patient with cellulitis did not show a flare reaction with 0.50 ma. but did with 0.52 ma. at 8:00, 12:00, 4:00 and 8:00 o'clock. The results in Table 11 show that the patient with cellulitis showed no flare reaction with 0.50 ma. on any one of 10 consecutive days, but did show a flare reaction at 0.52 ma. on each of 10 consecutive days.

THE EFFECT OF THE EXTERNAL ENVIRONMENTAL TEMPERATURE ON THE THRESHOLD OF THE FLARE REACTION

Our observations on the 913 subjects reported in Table 2 did not indicate that the variations in environmental temperature which occur at ordinary room temperature had any significant effect on the threshold of the flare reaction. Nevertheless, it was decided to collect some systematic data on the subject.

Accordingly, eight normal subjects were selected and the threshold of their flare reaction was determined by method III, along with the energy input, with a controlled room temperature of 70° F., 33° F., and 108° F.

The results are shown in Table 12. It will be noted that the threshold of flare as regards temperature was not influenced by environmental temperature. However, the amount of energy required to maintain the temperature of the applicator tip varied directly with the environmental temperature.

This would indicate, as is true of arteriosclerosis, that the rate of blood flow through the skin or the temperature of the skin are not important factors in determining the threshold of flare with this method.

TABLE 10

Variation of the threshold of flare and pain during one day apparatus model 2-A

NO.	DIAGNOSIS	SEX	AGE	THRESHOLD OF FLARE IN ma. 1/100 ma.			THRESHOLD OF PAIN IN ma. IN 1/100 ma.
1	Cellulitis	M	37	50: 0	52: 1, 2, 3, 4※	54: 1, 2, 3, 4※	66, 73, 62, 61*
2	Infected burn of face	M	34	46: 3	48: 1, 2, 3, 4	50: 1, 2, 3, 4,	50, 59, 56, 61
3	Frostbite amputation of both feet	M	44	46: 0	48: 1, 2, 3, 4	50: 1, 2, 3, 4	71, 75, 71, 66
4	Cancer of the esophagus	M	50	54: 0	56: 0	52: 1, 2, 3, 4	54, 53, 53, 46
5	Stasis leg ulcer	M	59	48: 2, 3, 4	50: 1, 2, 3, 4	52: 1, 2, 3, 4	65, 61, 65, 58
6	Rheumatic heart disease. Congenital failure	F	54	48: 0	50: 2, 3, 4	52: 1, 2, 3, 4	56, 50, 60, 56
7	Rheumatic heart disease. Decompensation	F	26	46: 0	48: 1, 2, 3, 4	50: 1, 2, 3, 4	47, 49, 58, 54
8	Recent C.V.A. Paralysis left side†	F	79	52: 0	54: 0	56: 1, 2, 3, 4	57, 64, 59, 56
9	O.H.D. Decompensation coronary occlusion	F	66	48: 0	50: 2	52: 1, 2, 3, 4	70, 65, 66, 70

※ The numbers give the time of the day, when a positive reaction was obtained; 1 = 8:00 am, 2 = 12:00 noon, 3 = 4:00 pm, 4 = 8:00 pm.

* Taken at 8:00 am, 12:00 noon, 4:00 pm, and 8:00 pm, respectively.

† This patient is now being checked for possible malignancy.

It was observed in a few tests that immersion of the arm immediately before the test for 5 minutes in either warm water (43° C.) or cold water (14° C.) raised the threshold.

THE EFFECT OF CERTAIN DRUGS ON THE THRESHOLD OF FLARE REACTION

From the viewpoint of the mechanism of the flare reaction, it was considered important to study the effect of certain drugs. Such empirical knowledge *per se*

TABLE 11

Variation of the threshold of flare and pain during 10 consecutive days (model 2A)

NO.	DIAGNOSIS	SEX	AGE	THRESHOLD OF FLARE IN ma. IN 1/100 ma.			THRESHOLD OF PAIN IN ma. IN 1/100 ma.
1	Cellulitis	M	37	50: 0※	52: 10	54: 10	Mean 66 s.e. 1.63
2	Infected burn of face	M	34	46: 0	48: 3	50: 10	Mean 55
3	Frostbite amputation of both feet	M	44	46: 0	48: 9	50: 10	Mean 65 s.e. 1.93
4	Cancer of the esophagus	M	50	54: 0	56: 6	58: 10	Mean 57 s.e. 2.74
5	Stasis leg ulcer	M	59	48: 0	50: 7	52: 10	Mean 59 s.e. 2.03
6	Rheumatic heart disease. Congenital failure	F	54	48: 0	50: 6	52: 10	Mean 57 s.e. 1.42
7	Rheumatic heart disease. Decompensation	F	29	46: 0	48: 8	50: 10	Mean 49 s.e. 1.29
8	Recent C.V.A. Paralysis left side*	F	79	52: 0	54: 2	56: 10	Mean 61 s.e. 2.31
9	O.H.D. Decompensation. Coronary occlusion	F	66	48: 0	50: 5	52: 10	Mean 64 s.e. 2.11

※ The figure gives the number of positive reactions at the indicated level.

* This patient is being checked for possible malignancy.

TABLE 12

Showing that the external environmental temperature of the patient has no effect on the flare threshold as regards the temperature of the applicator tip but does have an effect on the quantity of energy input

TEMPERATURE	NO. OF SUBJECTS	INSTRUMENT	FLARE		ENERGY INPUT	
			Mean ma.	Range ma.	Mean ma.	Range ma.
70° F. Room temp.	8	New Model B	0.53 S. e.* 0.01	0.50–.58	24 S. e. 1.82	18–32
33° F. Cold room	8	New Model B	0.53 S. e.* 0.013	0.50–.58	34 S. e. 2.84	26–44
108° F. Hot room	8	New Model B	0.53 S. e.* 0.01	0.50–.58	17 S. e. 1.61	13–20

* S. e., standard error.

is also important from the viewpoint of the interpretation of the test, since patients may receive drugs for therapeutic purposes, especially morphine for pain.

After determining the threshold of flare the subject was injected with a therapeutic or diagnostic dose of histamine, pyribenzamine, adrenalin, or morphine.

The results (Table 13) show that histamine (0.01 mg. per kg.) and adrenalin (0.25 cc. of 1:1,000 solution) did not change the threshold of skin flare, but had a marked influence on the energy required to obtain and maintain the threshold

TABLE 13

Showing the Effect of Systemic Injection of Certain Drugs on the Flare Reaction (8 normal subjects, New Model A)

	THRESHOLD OF SKIN FLARE (MA)	ENERGY IN MA		SIZE OF FLARE (MM)	
		Mean	S.e.	Mean	S.e.
Control	0.26	16.5	0.3	19.1	1.9
Histamine, (0.01 mg/kg)	0.26	19.2	0.4	21.6	2.1
Adrenalin, (0.25 cc 1:1,000)	0.26	16.2	0.3	19.6	1.7
Morphine, (10 mg)	0.30	21.5	0.5	22.1	2.4

TABLE 14

Showing the effect of an intradermal injection of certain drugs on the flare reaction at the site of injection

SUBSTANCE	NO. OF SUBJECTS	INSTRUMENT	SIZE OF FLARE IN DIAMETER IN mm.		ENERGY IN ma.	
			Mean	Range	Mean	Range
Saline 0.1 cc.	8	New Model A	32 S.e. 0.58	23–29	29 S.e. 1.80	27–31
Adrenaline 0.1 cc. 1:4000	8	New Model A	36 S.e. 1.43	32–41	27 S.e. 1.43	25–30
Histamine 0.1 cc. 1:4000	8	New Model A	46 S.e. 1.7	39–58	31 S.e. 1.91	29–32

temperature. The effect of adrenalin is not statistically significant. But the trend is clear, and a larger dose or a greater number of tests might decrease the energy unequivocally.

Pyribenzamine (100 mg. by mouth) did not influence the threshold in 8 subjects; a larger dose may do so.

Morphine sulphate (10 mg.) unequivocally raised the threshold. This effect of morphine was found only in this series and may influence some of the early results. Later on patients under morphine were excluded.

Table 14 shows that the intradermal injection of vaso-active drugs produces results comparable to those of their systemic effect.

Of the drugs tested in this series only morphine changed the threshold and could produce a quasi-malignant response.

OTHER OBSERVATIONS

A number of patients were studied for a prolonged period to determine the effect of various other factors. The results will be briefly summarized.

Surgery. An operation on a non-malignant condition had no effect on the threshold in 12 patients. In 14 patients on whom surgery was performed without removal of the tumor, the flare threshold was not significantly changed. In five patients it was found that general anesthesia raised the flare threshold. In 11 cancer patients in whom the surgical operation relieved pain due to pressure or obstruction the flare threshold was not affected. In 3 of 5 patients in whom orchiectomy for carcinoma of the prostate was performed and in whom pain was relieved and the clinical picture was otherwise improved, the flare threshold was decreased. In the remaining 2 the clinical condition was not benefited and the flare threshold was unchanged.

Fever had no significant effect on the flare threshold in 9 patients tested.

A blood transfusion temporarily lowered the threshold in 7 out of 8 patients with a carcinoma. Oxygen inhalation may also lower the flare threshold.

Steroid Therapy. In 11 patients with carcinoma of the prostate, steroid therapy improved the clinical condition and decreased the flare threshold in 6. In 5 patients who had carcinoma of the breast and had received steroid therapy the flare threshold was decreased in all and definite clinical improvement occurred in five.

X-ray Therapy. A single x-ray treatment was followed by a decrease in the flare threshold in 3 out of 34 cases, and a complete series of treatment in 5 out of 14 cases.

ON THE MECHANISM OF THE ELEVATED THRESHOLD OF FLARE IN PATIENTS WITH MALIGNANT DISEASE

Lewis (1) has extensively studied the mechanism of cutaneous flare in response to various types of noxious excitants. His observations indicate that the red reaction or "red spot," which occurs directly under the site of application of the noxious excitant, is due to a dilation of the minute vessels of the skin and does not involve any significant change in blood flow. The surrounding flare reaction, on the contrary, is due to a dilation of arterioles which results in a forward movement of blood. The dilation of the arterioles is due to an axon reflex because a flare reaction occurs for several days after the nerve supply to an area of the skin has been cut but not after the nerve has degenerated. Lewis has also presented strongly presumptive evidence showing that the axon reflex, which causes flare, is excited by the release of histamine or an H-substance. It is quite certain that histamine or a histamine-like substance is released when the skin is irritated to produce an extensive flare because gastric secretion is stimulated (7, 8).

It should be pointed out that Lewis (1) has reported that in urticaria the skin is more susceptible to mechanical injury, as regards the production of flare and

a wheal, than to thermal, chemical, or electrical injury. If this is true, then the elevated heat flare threshold in cancer is not analogous to a condition opposite to that of urticaria, i.e. a condition in which the skin is less susceptible to injury. Nevertheless, it is possible that the incidence of urticaria and allergic states may be lower in the cancer than in the noncancer patient.

On the basis of what is known regarding the mechanism of the flare reaction, the threshold of the reaction could be elevated in the following ways:

I. A relative inadequacy of H-substance, due to:
   A. Decrease in production caused by a deficiency of the cellular enzymes which releases histamine.
   B. Increase in rate of destruction of the released histamine by histaminase.

II. An increase in the threshold of stimulation of the sensory nerve ending or of the axon reflex.

III. Arteriolar Hypertonus, due to:
   A. Increased vasoconstrictor nervous tone.
   B. Vasoconstrictor substance in the circulation released by cancer cells or by effect of cancer cells on adjacent or distant body cells.
   C. Abnormality of acetylcholine-cholinesterase system in the arteriole (Dale), or some abnormality of the motor-effector limb of the axon reflex.

(I) A decrease in production of H-substance could result from a deficiency of the proteolytic enzyme which releases histamine on the application of a pain stimulus or on tissue injury (7, 8, 9). If the histaminase content of the skin were increased, the histamine or H-substance released would probably be destroyed more rapidly. In either case, a more intense noxious stimulus would be required to cause a flare reaction. (II) The only evidence in support of an increase of threshold of the nervous excitation or transmission is that morphine which, as is well known, has some peripheral action on blood vessels increases the threshold of flare. Also with advancing age there is an increase in threshold of both cutaneous pain and flare, as shown above. (III) If there is an increase in arteriolar tone, a more intense stimulus would be required because more H-substance would have to be released to stimulate more intensely the sensory endings of the axon reflex to produce the greater than normal amount of acetylcholine which would be required to cause arteriolar dilation.

The foregoing presentation is only a partial analysis of the problem, but it is probably adequate for the interpretation of the results to follow.

The Threshold of the Histamine Flare in Subjects With and Without Cancer. It was thought that the determination of the threshold of the histamine flare in subjects with and without cancer would throw some light on the foregoing analysis, of the mechanism of the elevated flare threshold in subjects with cancer.

Accordingly, 20 subjects with and without cancer were injected intradermally with 0.1 cc. of a normal saline solution containing a concentration of histamine phosphate varying from 1:100,000 to 1:1 million.

The results are shown in Table 15. A Chi square analysis of the data show

that the differences are statistically significant; so, we may be reasonably certain that the histamine flare threshold is higher in a group of subjects with cancer than without cancer. However, a clear cut line of demarcation between the threshold of the subject with and without cancer was not found. Apparently the heat threshold of flare is either more critical or more sensitive due to ease of control than the intradermal histamine flare.

Our interpretation of these observations is as follows: (IA) Since a known concentration of histamine was injected, the factor of a deficiency of production was controlled in the foregoing experiment. However, it is reported that the anti-proteolytic (antichymotryptic) activity of the serum is elevated in the

TABLE 15

Flare reaction to histamine phosphate in normal saline solution when 0.1 cc. was injected intradermally into 20 subjects with and 20 without cancer

HISTAMINE CONCENTRATION USED	SUBJECTS GIVING A POSITIVE FLARE RESPONSE				DIFFERENCE	
	20 subjects without cancer		20 subjects with cancer			
	No.	%	No.	%	No.	%
1:100,000	20	100	16	80	4	20
1:200,000	19	95	15	75	4	20
1:300,000	19	95	12	60	7	35
1:400,000	19	95	8	40	11	55
1:500,000	17	85	6	30	11	55
1:600,000	13	65	4	20	9	45
1:700,000	11	55	3	15	8	40
1:800,000	8	40	1	5	7	35
1:900,000	7	35	1	5	6	30
1:1 million*	7	35	0	0	7	35
Mean threshold concentration	1:700,000		1:345,000			

* Control tests on 10 persons using normal saline solution did not cause a flare reaction. Chi square analysis of the two groups yielded a probability of less than 0.01.

cancer patient. Unfortunately, this is not specific for the cancer patient (10, 11), and hence cannot be correlated with the apparently high degree of specificity of the heat flare reaction we have observed. (IB) If there were an increase in the histaminase in the skin of the cancer patient, then, even though a known concentration of histamine was injected, it could be destroyed faster, and hence a higher concentration would be required. This possibility is unlikely because in human pregnancy the serum histamine is increased 1,000 times, but we found the heat flare threshold to be normal (Table 3) and Wicksell (12) found the histamine flare to be normal in uncomplicated pregnancy. (III) Since we can find no significant evidence to support the possibility that there is an inadequacy of H-substance produced by the skin of the cancer patient, we are inclined to believe that an arteriolar hypertonus exists in the skin of the cancer

patient. (IIIA) There is no evidence supporting increased vasoconstrictor-nerve tone in the cancer patient. (IIIC) Arteriolar hypertonus in cancer would appear not to be due to a disturbance of the acetylcholine-cholinesterase mechanism because the flare test is normal in complicated pregnancy, and estrogens which are present in large quantities in uncomplicated pregnancy stimulate the production of cholinesterase (13, 14). (II) Although our evidence on the effect of morphine and ageing on the threshold of flare and pain indicate that the theshold of the sensory limb of the axon reflex may be raised in the cancer patient, we are at present inclined to interpret our evidence and that obtainable in the literature as indicating that the high threshold of flare in the skin of the cancer patient is due to a circulating vasoconstrictor substance, such as "pitressin for a lack of a better analogy (15). The presence of a normal flare threshold in the cancer patient, after sex hormones are given, or when substances are absorbed from a suppurating cancer, both of which are vasodilating (16a), support the presence of an arteriolar hypertonus. Table 16 shows the results of intradermal injections of Acethylcholine Chloride (Merck). As the vasodilation caused by this substance is due to a direct effect on the blood vessels, this could be a test for the presence of a vasoconstrictor substance in the blood of the cancer patient. Though the difference observed between the two groups (Table 16) is not statistically significant the trend suggests that a significant difference might be obtained by the use of a more refined technique.

TABLE 16

The figures in the table give the number of subjects with a positive response (10 cancer patients, 10 controls)

CONCENTRATION OF ACETYLCHOLINE*	WITHOUT CANCER	WITH CANCER
1:100	10	9
1:1,000	8	6
1:10,000	5	3
1:100,000	3	2

The difference between the two groups is not statistically significant.

* Acetylcholine chloride (Merck) given intradermally. Only a fresh solution was used and it was used within two hours after it was made.

Source and Nature of the Vasoconstrictor Substance. If a vasoconstrictor substance is produced in the presence of cancer, two questions arise: (A) What is the course of the substance? and, (B) Why does not a rise in blood pressure occur in the cancer patient?

The source might be from the cancer cell, or from the aseptic necrosis of normal body cells due to the invasion of the cancer cell, or to the effect of the cancer on some organ such as the posterior lobe of the pituitary gland or adrenal. The only instance where it is known that a vasoconstrictor substance is released as the result of asceptic necrosis, and frequently without a rise in blood pressure, is the early pre-eclamptic state. It is unknown whether the constrictor substance comes from the dying or dead trophoblast or from the effect of the

entrance of large amounts of thrombokinase which enters the blood (16b) and on reacting with the blood platelets releases a vasoconstrictor substance (17). According to this supposition the skin flare should be elevated in eclampsia and we have found it to be elevated in 5 of 7 patients examined to date by us. An increase of pituitrin in the circulation should also increase the threshold of flare according to the observations of Krogh (15) and of Lewis (1). However, no tendency toward the production of concentrated urine by the cancer patients has been observed.

Like all effects of phenomena when first observed, the cause or causes of the elevated threshold of flare in the cancer patient is conjectural and the possibilities numerous.

GENERAL DISCUSSION

It is remarkable that a vasomotor skin reflex should be modified similarly and to some extent quantitatively by various types of malignant neoplastic disease. Moreover, it appears that if the cancerous growth is temporarily inhibited or removed the effect disappears. Yet, all of those optimistic persons, who are working to find a non-morphological general diagnostic test for cancer, base their hope on the belief that there is something physiologically unique and characteristic about cancer or its effect on the host.

Is this effect of malignant growth due to the production by the cancer cell of a substance which affects the vascular reflex? Or, is it due to an indirect effect induced by the cancerous growth? In answer to the first question, we know that the ovarian granulosa cell tumor of the mouse exerts an effect on the capillary vessels of the liver and some other organs (18). In this case the possible presence of the hormone was easily recognized; could not have been missed, and was easily identified. May not cancer cells give off an arteriolar constrictor substance which would function to divert blood away from normal tissue to itself to insure its own growth. In answer to the second question, it is known that the adrenal gland is secondarily affected in tumor bearing animals and that cancer has other effects on the host (19).

The majority of the patients who had a proven cancer and were tested by us had a cancer that was well advanced but few were in the terminal stage of the disease. It remains to be determined how far advanced the cancer must be before it causes a specific elevation in the threshold of skin flare. We only can say that in the skin cancers we have seen, the flare threshold was not abnormally elevated until the cancer had metastasized. But, whenever a physiological difference between a cancer and non-cancer host is observed, another opportunity for an attack on cancer is provided.

SUMMARY

When an adequate degree of heat is applied to a small area of skin (forearm or back) a reddening or a flare occurs about the site of contact. An apparatus and method for its use is presented which allows the determination of the temperature and energy input required to produce a flare reaction. In normal sub-

jects and in patients without cancer the temperature required to produce a flare reaction when the heat was applied to an area 3 mm. square ranged from 44° to 45.4° C.

The threshold of skin flare, when heat is the noxious excitant, did not vary significantly in the same person under standard resting conditions during the day and over a period of 10 days. Sex and room temperature do not affect the threshold of flare. Age significantly increases the threshold of cutaneous flare and pain up to the age of 60 after which a plateau occurs.

In 77 normal persons, 32 patients with proven benign tumors, and 340 patients with various non-neoplastic diseases, the flare reaction was obtained within the normal temperature range of from 44 to 45.4°. In 349 patients with proven malignant neoplastic disease the temperature required to produce flare was 45.8° C. or higher in all but 14, including 4 patients with superficial cancer of the skin and 6 with pyogenic infection of the cancer. The effect of age on the flare reaction is not as great as that of cancer. Severe arteriosclerosis and marked anemia render the reading of flare difficult and may yield a value within the cancer range.

Steroid therapy is followed by a flare reaction within the temperature range indicating the absence of malignant neoplastic disease. Most patients who are clinically improved, and 15 of 16 patients who were "1 to 5 year surgical cures" showed a lower flare response. X-ray therapy in some patients caused the flare reaction to fall to the range indicating the absence of malignant neoplastic disease.

The presence of malignant neoplastic disease increases significantly the threshold of histamine flare. A concentration of histamine which uniformly differentiates between persons with and without cancer was not found.

The mechanism concerned in the elevation of threshold of cutaneous flare in the presence of cancer is discussed.

Much more study will be required to determine the possible value of "the effect" we have discovered for the diagnosis and therapeutic prognosis of malignant neoplastic disease.

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